

Docket No.: IBIS-0007 Filed. May 12, 1998 076,404 llation of Molecular Interaction Sites on RNA and Other Biomol Inventors, ricker et. al. Attorney: Jeffrey H. Rosedale Phone (215) 568-3100 Sheet 1 of 59

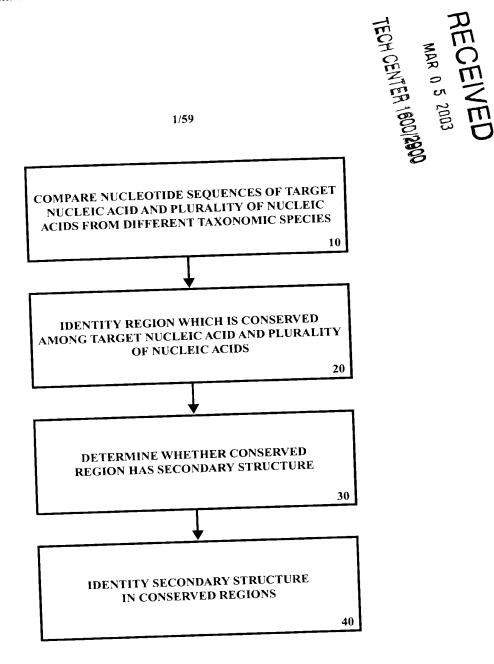
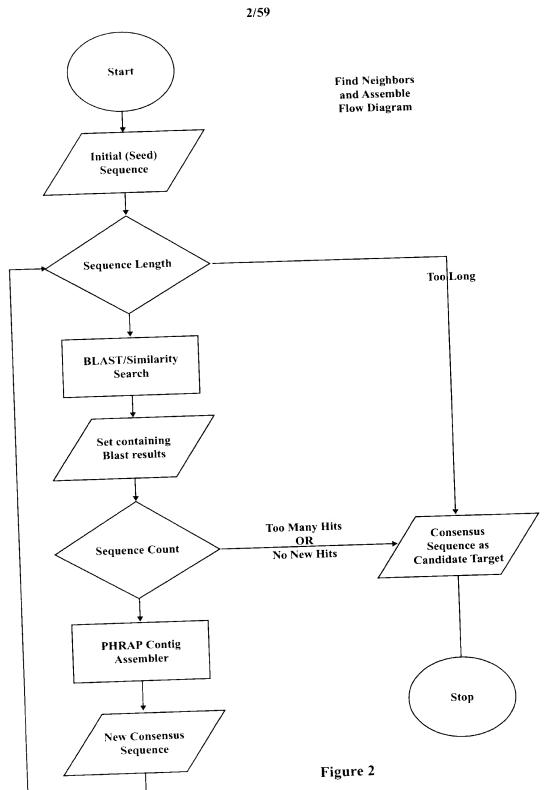


FIGURE 1

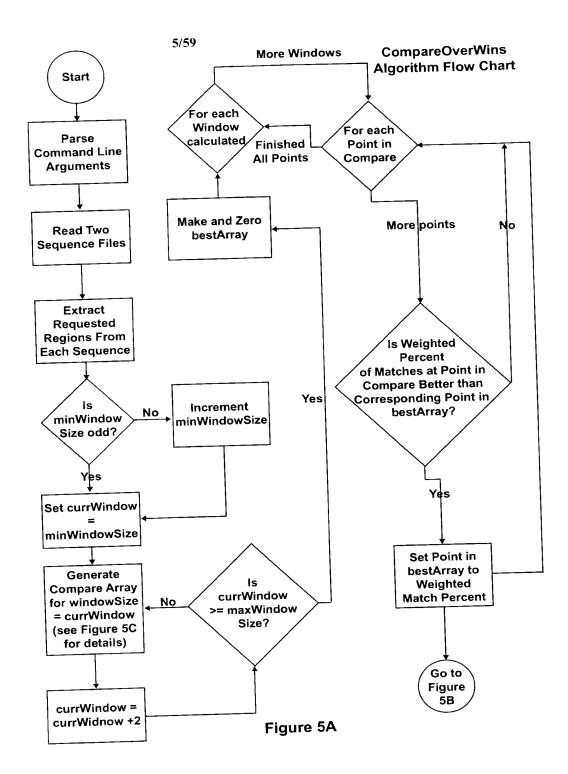


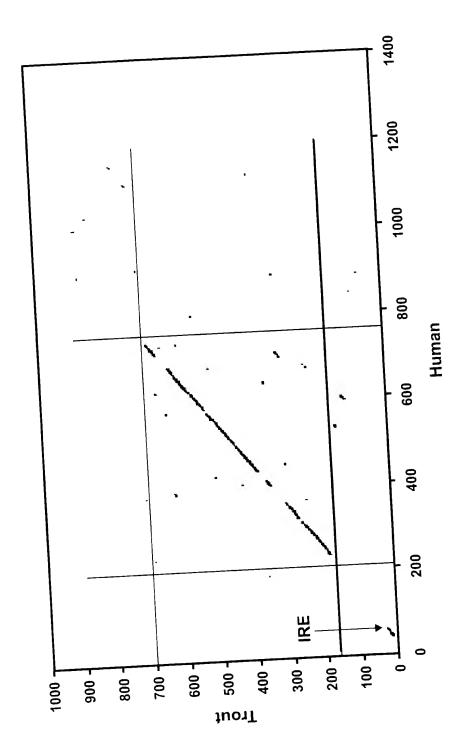
Docket No.: IBIS-0007
App 19 976,494
File Valuation of Molecular Interaction Sites on RNA and Other Biomor Inventors: Ecker et. ali.
Attorney: Jeffrey H. Rosedale
Sheet 2 of 59



Docket No., IBIS-0007 Filed: May 12, 1998 .: 09 076,404 Modulation of Molecular Interaction Sites on RNA and Other E Inventors Ecker et. al. Phone: (215) 568-3100 Attorney: Jeffrey H. Rosedale

Sheet 5 of 59





igure 11

Phonel (215) 568-3100

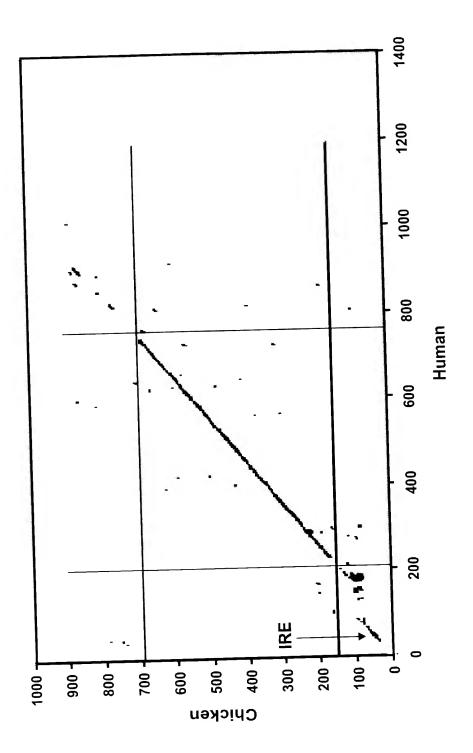


Figure 12

15/59

G U C C C G-U U-A C U-A U-A U-A C-G		ON	ON	9	YES	YES	YES	ON	
6 U G C C C C C C C C C C C C C C C C C C		ON O	Q N	Q.	YES	YES	2		
G-U A G C U A-U C-G U-A U-A C G-C U-G U-G U-G FROG		YES	YES	YES	YES	ON			
G-U A-U A-U C-G U-A U-A U-A U-G U-G S-C		YES	YES	YES	ON				
G-U C C A-U C-G U-G G-C U-G C-G C-G		YES	YES	9					
G-U A-U A-U C-G U-A U-A C-G C-G C-G C-G MAMSTER	RAT	ON	ON						
G-U G-C C C C C C C C C C C C C C C C C C C	<u>ත</u>	ON.							
		HUMAN	HAMSTER MOUSE	RAT	CHICKEN	SALMON	FROG	FLY	MOSQUITO

Figure 13

Docket No.: IBIS-0007 Filed: May 12, 1998 ilation of Molecular Interaction Sites on RNA and Other Biomo Inventors: Ecker et. al. Attorney: Jeffrey H. Rosedale Sheet 16 of 59 Phone: (215) 568-3100

16/59

Compound CI

$$\begin{array}{c|c} H_3C & CH_3 \\ H & O \\ N & - S \\ O & H & O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ \end{array} \\ \\ \begin{array}{c} O \\ O \\ \end{array} \\ \\ \begin{array}{c} O \\ O \\ \end{array} \\ \begin{array}{c} O \\ O \\ \end{array} \\ \\ \begin{array}{c} O \\ O \\ \end{array} \\ \\ \begin{array}{c} O \\ \\ O \\ \end{array} \\ \begin{array}{c} O \\ \\ O \\ \end{array} \\ \begin{array}{c} O \\ \\ \\ \end{array} \\ \begin{array}{c} O \\ \\ \\ \\ \end{array} \\ \begin{array}{c} O \\ \\ \\ \end{array} \\ \\ \begin{array}{c} O \\ \\ \\ \\ \end{array} \\ \begin{array}{c} O \\ \\ \\ \\ \end{array} \\ \begin{array}{c} O \\ \\ \\ \\ \\ \end{array} \\ \\$$

 $C_{12}H_{18}N_2O_5S$

$$\begin{bmatrix} H \\ HO \\ N \\ O \\ HO \end{bmatrix} \begin{bmatrix} O \\ O \\ HO \\ O \\ H \end{bmatrix} \begin{bmatrix} O \\ O \\ O \\ O \\ H \end{bmatrix} = OCH_3$$

$$F_i \qquad F_{ii} \qquad F_{iii}$$

Molecular Formula

H₂NO C₅H₉NO

 $C_7H_7O_3S$

Figure 14

TECH CENTER 1600/2900

RECEIVED



Docket No.: IBIS-0007

A \$\times 09 076,404\$ Filed May 12, 1998
10 dulation of Molecular Interaction Sites on RNA and Other Bio
Inventors: Ecker et. al.
Attorney, Jeffrey H. Rosedale
Sheet 17 of \$9

17/59

Addition of fragments to yield compounds

	Table						
Fragment Identifier	Structure	Name	Molecular formula	Other			
Fi	H-O-N-	Hydroxylamin	e H ₂ NO				
Fii	H ₃ C CH ₃	Amino acid	C₅H ₉ NO				
F _{iii}	0 	_{CH3} Sulfonyl	C ₇ H ₇ O ₃ S				

Figure 15

TECH CENTER 1600/2900

Phone: (215) 568-3100

Reagents	Identifier	Name	Properties
H-O-NH ₂ or P-O-NH ₂	R _i	Hydroxylamine	
H ₃ C CH ₃ HO N-FMOC	R_{ii}	FMOC blocked amino acid	
OCH ₃	R _{iii}	Sulfonylchloride	
P = solid support			

Figure 16



Docket No.: IBIS-0007 No.: 09 076,404 Modulation of Molecular Interaction Sites on RNA and Other i entors: Ecker et. al.

Phone: (215) 568-3100 Attorney: Jeffrey H. Rosedale Sheet 19 of 59

19/59

Transformation

Figure 17



20/59

Common Fragment/Different Reagents and Transformations

Figure 18



21/59

Common Fragment/Different Reagents and Transformations

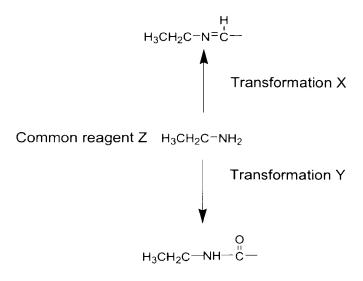


Figure 19A



Docket No. IBIS-0007 No. 09 076,404 No. 09 076,404 Filed. May 12, 1998 Modulation of Molecular Interaction Sites on RNA and Other I Inventors: Ecker et. al Attorney: Jeffrey H. Rosedale Sheet. 22 of. 59 Phone: (215) 568-3100

22/59

Common Reagent

$$\begin{array}{c|c} & H_3C & \longleftarrow_{CH} & \\ & & \end{array}$$
 Transformation X'
$$\begin{array}{c|c} & O & \\ &$$

Figure 19B

Inventors; Ecker et al. Attorney: Jeffrey H. Rosedale Sheet 23 of 59

Phone; (215) 568-3100

TECH CENTER 1600/2900

23/59

Symbolic addition of fragments to yield compound

Symbolic Structure	Symbolic Identifier	Molecular formula
Fragment		
$\sum x$	$\mathbf{F_{i'}}$	$C_uH_vN_w$
<u> </u>	F _{ii'}	$C_uH_vN_w$
х —О— Y	F _{iii'}	$C_uH_vN_w$
Compound		
	CI'	$C_u H_v N_w \dots$
		Molecular formula F _{i'} +
		Molecular formula F _{ii'}
		Molecular formula Fiii'
		= Molecular formula CI'

Figure 20



Docket No. IBIS-0007

App. 109 076,404 Filed May 12, 1998

Fille Julation of Molecular Interaction Sites on RNA and Other Biomol Inventors: Ecker et al.,

Attorney Jeffrey H Rosedale Phone (215) 868-3100

Sheet 24 of 59

24/59

Symbolic Reagent Table

Identifier	Name	Structure	Molecular formula
R1	xxx	∠CI	xxx
R2		CNO	
R3	•••	CI	
R4	•••	Br	
R5		Br Br	
R6		Pg—O—OEt	
R7		Pg——CI	
R8	•••	Pg——Br	
R9		Pg1 N3 — Pg2	
R10		Pg1 N3 Pg2	

Figure 21



Docket No.: IBIS-0007 App 59 076,404 09 076,404 Filed: May 12, 1998 dulation of Molecular Interaction Sites on RNA and Other Biom Inventors: Ecker et. al. Attorney, Jeffrey H. Rosedale Sheet 25 of 59

Phone. (215) 568-3100

25/59

Symbolic Fragment Table

<u>Identifier</u>	Symbolic Sturcture	Molecular Formula	Molecular Weight
F1	∠ X	xxx	xxx
F2	<u></u> х		
F3	○ -x		
F4	x x		
F5	X—O—Y		
F6	X——Y		
F7	x − z		
F8	x Z		



26/59

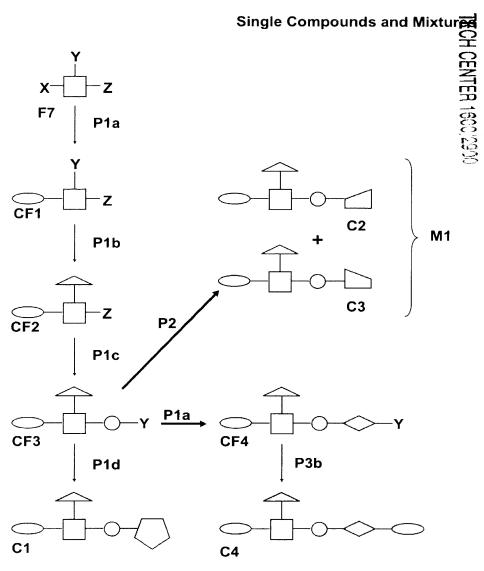
Symbolic Transformation Table

Identifier		Symbolic Re	actions		Reagent
T1	F1	X		R1	conditions α
T2	F2	<u></u> х		R2	conditions $\boldsymbol{\beta}$
Т3	F3	○ -x		R3	conditions α
Т4	F3	\bigcirc -x		R4	conditions α
Т5	F4	x x	-	R5	conditions α
Т6	F5	X—O—Y	←	R6	conditions $\boldsymbol{\epsilon}$
Т7	F5	X—O—Y		R7	conditions $\boldsymbol{\alpha}$
Т8	F6	X——Y	4	R8	conditions α
Т9	F7	x-L-z	4	R9	conditions γ
T10	F8	$x \stackrel{Y}{\longleftrightarrow}_z$		R10	conditions γ

Inventors: Ecker et al... Attorney: Jeffrey H. Rosedale Sheet 27 of 59

Phone: (215) 568-3100

27/59



P = synthetic path

CF = complex fragment

F = fragment

M = mixture

C = compound

Figure 24



Docket No.: IBIS-0007
No.: 09 076,404
Eiled: May 12, 1998
C: Modulation of Molecular Interaction Sites on RNA and Other
Inventors: Ecker et. al.
Attorney: Jeffrey H. Rosedale
Sheet. 28 of 59
Phone: (215) 568-3100

28/59

Mixture 2

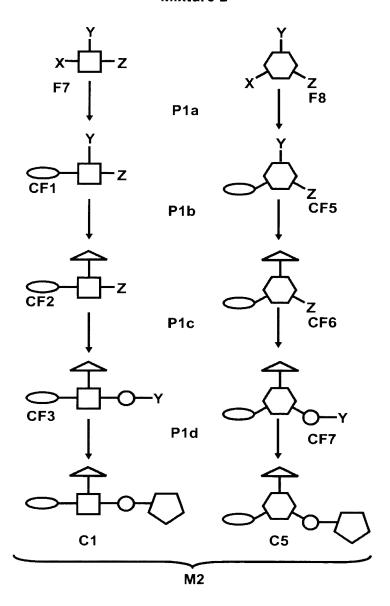


Figure 25



29/59

Mixture 3

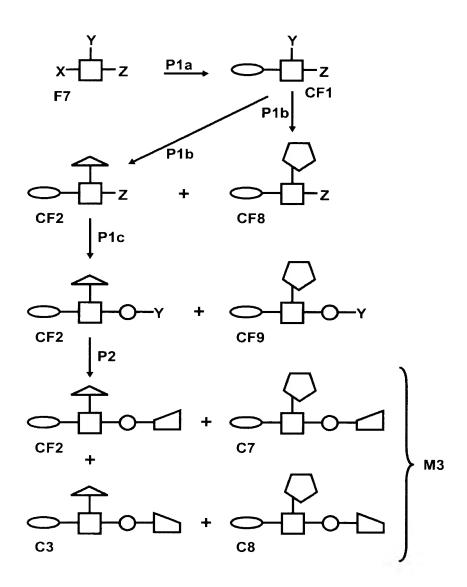


Figure 26





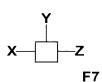
Inventors: Ecker et al. Attorney Jeffrey H Rosedale Sheet 30 of 59

Phone (215) 568-3100

30/59

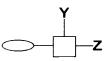


2 Starting Fragments

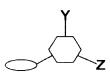


x Z F8

2 Complex Fragments

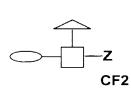


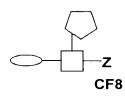
CF1

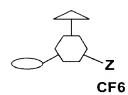


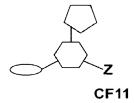
CF5

4 Complex Fragments



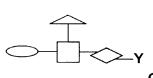






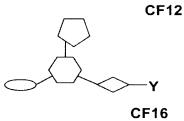
8 Complex Fragments

CF9



CF13

CF15



CF7

CF14

Figure 27A





Phone (215) 568-3100

31/59

Mixture 4 (continued)

16 compounds

Figure 27B



Docket No.: IBIS-0007 n: 09 076,404 Filed, May 12, 1998 Modulation of Molecular Interaction Sites on RNA and Other Bio hivehtors: Ecker et. al. Attorney: Jeffrey H. Rosedale Sheet 32 of 59 Phone: (215) 568-3100

32/59

Tracking Table for Compound C1

(a) By Fragments:

n	n+1	n+2
F7		
	F2	
	F1	
1	F5	
		F3

($(a) \underline{B}$	y Transf	ormations:				
	Syn	thesis P	ath 1	S	yr	thesis P	ath 2
	n	n+1	n+2	n		n+1	n+2
	Т9			T	9		
		T2				T2	
		T1				T1	
		Т6				T7	
			T3				T3
	Syr	ıthesis P	ath 3	S	yı	ıthesis P	ath 4
	n	n+1	n+2	_n		n+1	n+2
	Т9			Т	9		
		T2				T2	
		T1				T1	
		Tr.				T.7	

Figure 28



Docket No. IBRS-0007
No.: 09 076,404
Enled: May 12, 1998
Modulation of Molecular Interaction Sites on RNA and Other Enled: Inventors, Ecker et al.
Attorney: Jeffrey H. Rosedale
Sheet 33 of 59

33/59

Tracking Table

Tracking M1

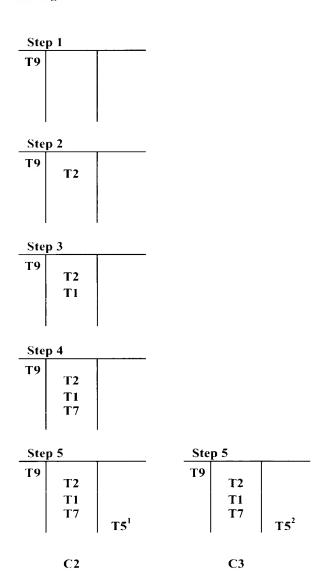


Figure 29



et No.: IBIS-0007 09 076,404 Filed: May 12, 1998 Modulation of Molecular Interaction Sites on RNA and Other Bi Inventors: Ecker et. al. Attorney: Jeffrey H. Rosedale Sheet 34 of 59

Phone: (215) 568-3100

RECEIVED
MAR 0 5 2003

TECH CENTER 1600 22900

34/59

Tracking Table

Tracking M2

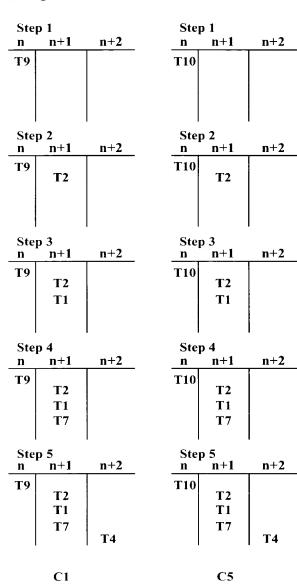


Figure 30



cket No i IBIS 0007 No:: 09/076,404 No. 09 0°6,404 I filed May 12, 1998 Modulation of Molecular Interaction Sites on RNA and Other Inventors: Ecker et. al Attorney Jeffrey II. Rosedale Sheet. 35 of. 59

Phone: (215) 568-3100

35/59

Tracking Table

Tracking M3

Step 5

T2

T1

T7

C2

 $T5^1$

Step 3
T9 T2 T3
Step 4
T9

Step 5

Т9

T2

T1

Т7

C3

Figure 31

T5²

Step 5

T9

T2

T3

T7

C7

T51

Step 5

Т9

T2

T3

T7

C8

T5²

OIP

FEB 2 7 2003

TRADEMARY

Dock C No., IBIS 0007

App 1076,404 Filed May 12, 1998

Title dilation of Molecular Interaction Sites on RNA and Other Biomol Inventor - Feker et al.

Attoric - Jeffrey H. Rosedale Phone (213) 568-2100

Sheet 100-59

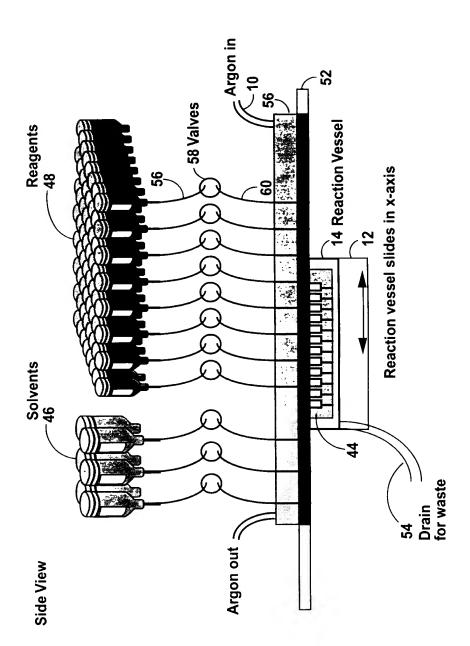


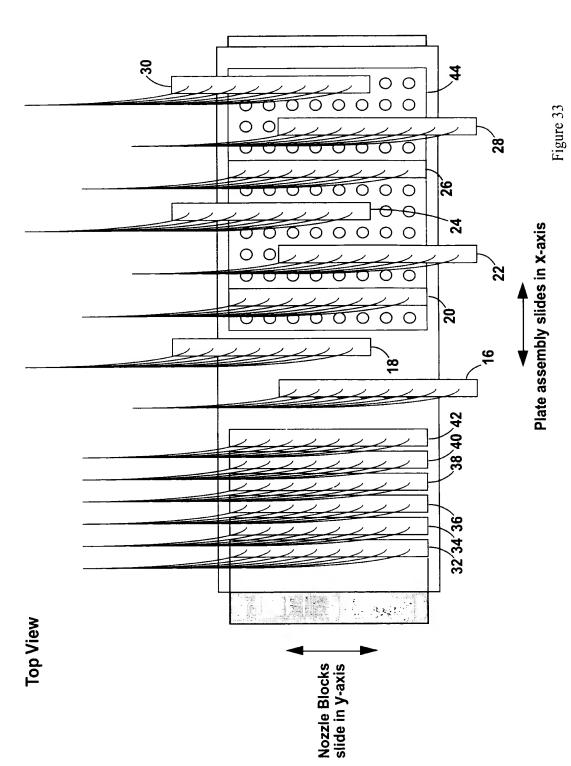
Figure 32



Docks No.: IBIS-0007 App. 19 076,404 Filed, May 12, 1998 Title: Adulation of Molecular Interaction Sites on PMA and Other Biometrics: Ecker et. al.

Inventors: Ecker et. al Attorney: Jeffrey H. Rosedale Sheet 37 of 59

Plane (215) 568-31m





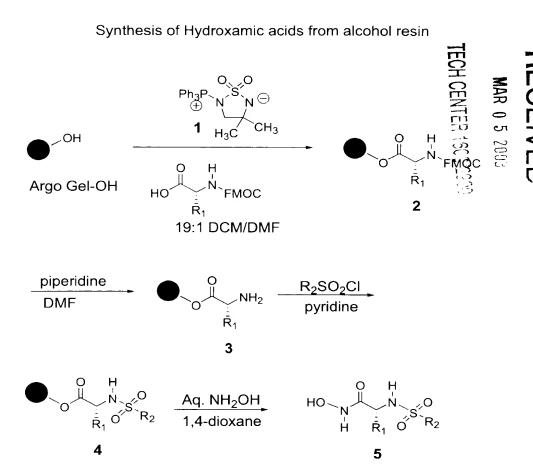


Figure 34



ket No. 1BIS-0007 No. 09 076,404 Filed May 12, 1998 Modulation of Molecular Interaction Sites on RNA and Other B

Inventors Ecker et al Attorney Jeffrey II Rosedale Sheet 39 of 59

Phone (215) 568-3100

39/59

Synthesis of hydroxylamine resin

Figure 35



Dock No. IBIS-0007

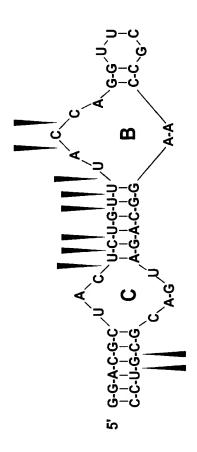
App. 19 076,404

Filed May 12, 1998

Intel sodulation of Molecular Interaction Sites on RNA and Other Brond Inventors. Ecker et. al.

Attorney Jeffrey H. Rosedale. Phone. (215) 568-3100.

Sheet. 40 of. 59





Docket No. 1BHS-0007

Apr. 109 076,404

Titles dulation of Molecular Interaction Sites on RNA and Other Biom Inventors: Ecker et. al.

Attorney, Jeffrey H. Rosedale
Sheet 41 of 59

IC ₅₀ (µM)	2	2 >	< 50
Calc. ∆G of binding (kcal/mole)	-5.1	5.	-5.1
Structure 0	Z-O-Z	ZI	0=0
ACD Code	00001199	00192509	00003934



Docket No. IBIS-0007

App N. 1076,404

Titled May 12, 1998

Title New atton of Molecular Interaction Sites on RNA and Other Biomolecular Inventors. Ecker et. al. Attorney. Jeffrey H. Rosedale. Phone. (215) 868-3100

Sheet. 42 of. 59

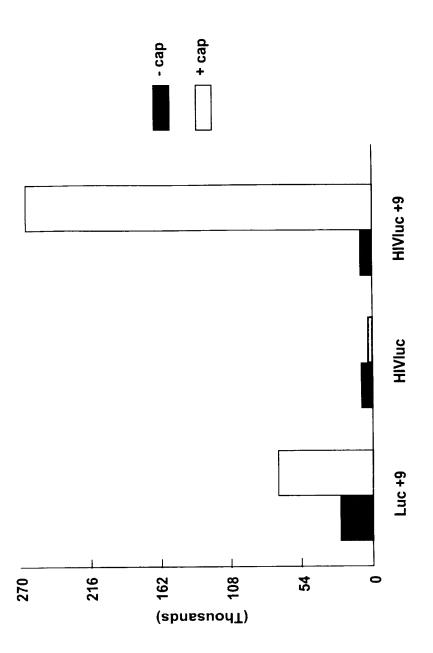


Figure 38A

Doc No IBIS-0007

Apr 100 00 076,404

Filed May 12, 1998

Interpolation of Molecular Interaction Sites on RNA and Other Bron less Inventors: Ecker et. al.

Attorney: Jeffrey H. Rosedale
Sheet 43 of 59

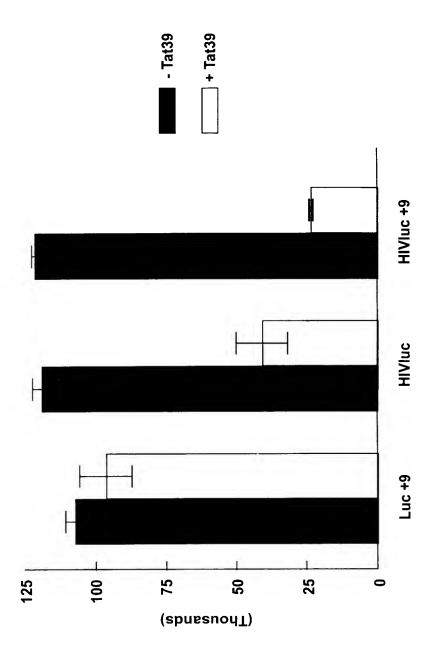


Figure 38B



Docket No., 1918, 6007

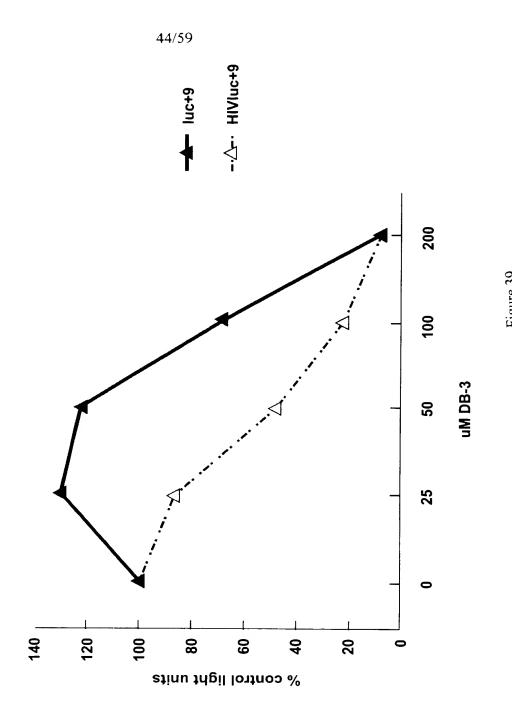
App No. (1997)

A4 Filed May 12, 1998

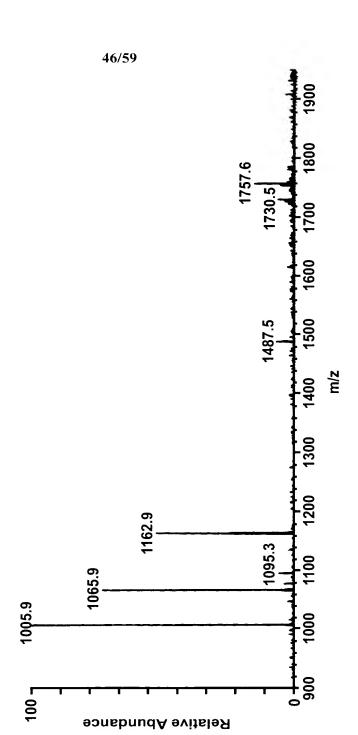
Intermotors: Ecker et. al.

Attorney: Jeffrey H. Rosedale

Sheet 44 of \$9



Docket No.: IBIS-0007.
App No.: 0 1 404 Filed, May 12, 1998
Little: Modit and Molecular Interaction Sites on RNA and Other Biomolecule:
Inventors: Ecker et. al.
Attorney: Jeffrey H. Rosedale Phone (215) 568-3100
Sheet: 46 of: 59



TECH CENTER 1600/2900

Figure 41A

RECEIVED



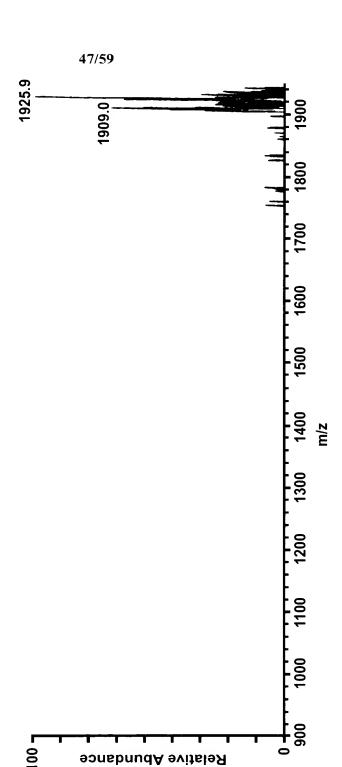


Figure 41B



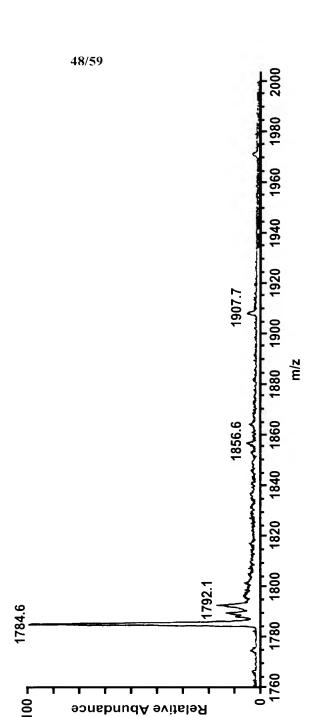


Figure 42A



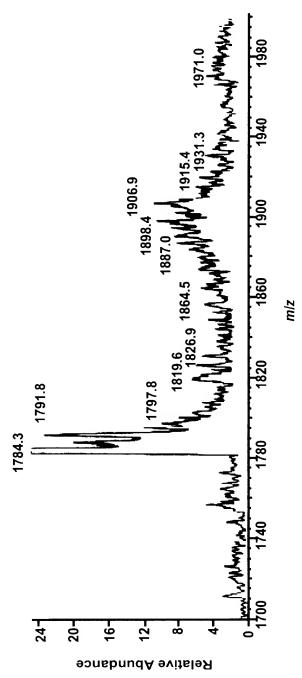
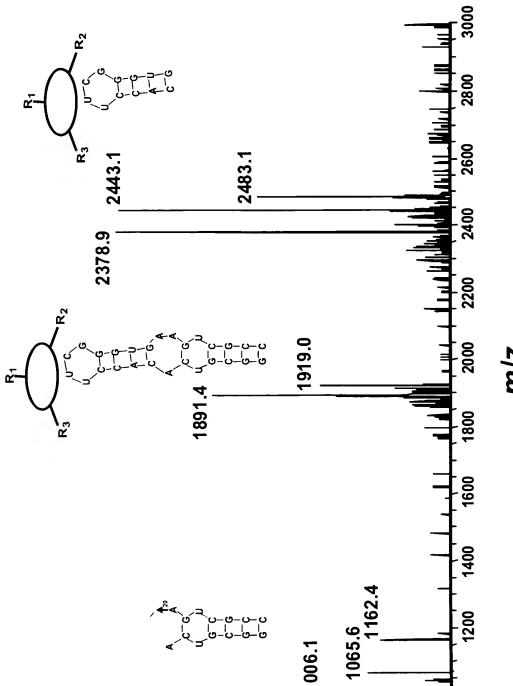


Figure 42B



Relative Abundance

FEB 2 7 2003 TRADEN

Docket No.: IBIS-0007

Ap. 109.076,404

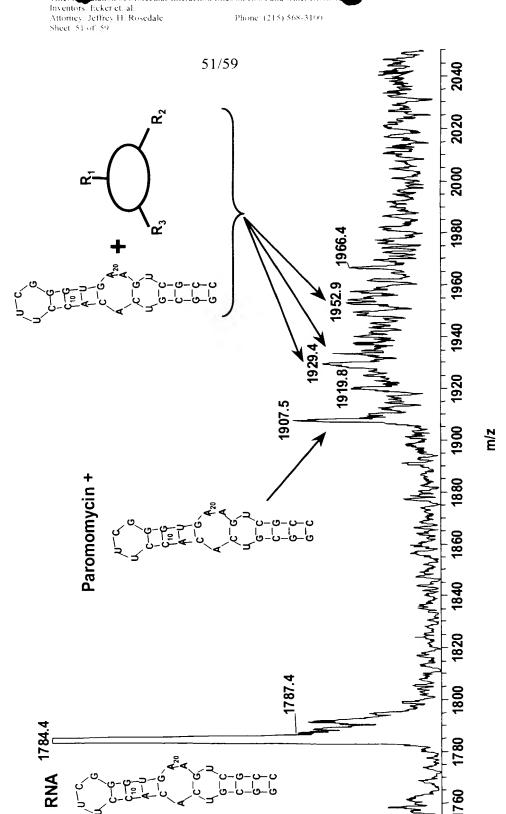
Filed May 12, 1998

Into odulation of Molecular Interaction Sites on RNA and Other Bion Inventors. Ecker et al.

Attorney: Jeffrey H. Rosedale

Slicet 50 of 59

Docket No. IBIS-0007 App Scott 1976,404 Filed May 12, 1998 Title, A. Jahon of Molecular Interaction Sites on RNA and Other Bromol. Inventors, Ecker et. al.



5

8

9

Ŋ

45

6

35

30

25

Relative Abundance

Figure 44

52/59

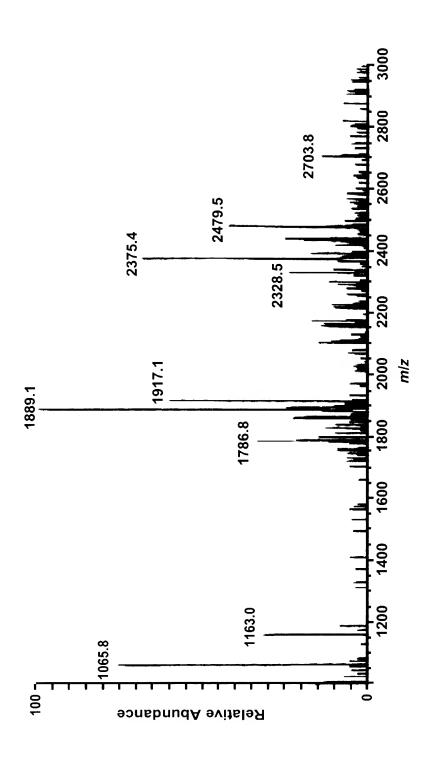
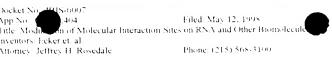
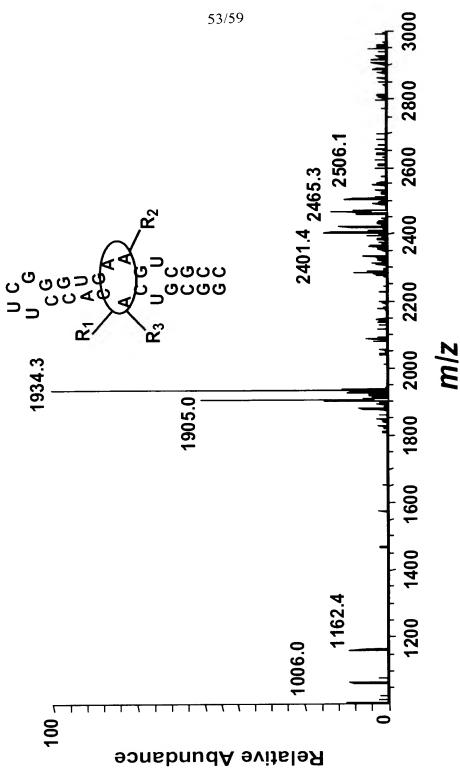


Figure 45







Significant 46